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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,846	10/14/2003	Mark Selby	2300-1676.001	3512

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/684,846	SELBY ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *5-9,12-14,17-19,22-26 and 32-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10,11,15,16,20,21 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/26/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-39 are pending.

Election/Restrictions

1. Applicant's election of group I, subgroup (A) and (i), which include claims 1-4, 10, 11, 15, 16, 20 and 27-31 in the reply filed on 11/25, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-4, 10, 11, 15, 16, 20 and 27-31 are considered before the examiner.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 1, 10-11, 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating Huh-7 cell line comprising PKR Arg ^{296} dominant negative disabling mutation and HCV sub-genomic replicon, wherein said cell is able to enhance the replication of sub-genomic HCV, does not reasonably provide enablement for generating any cell line comprising any kind of dominant negative disabling mutation and any viral sub-genomic replicon, wherein said cell is able to increase any anti-viral response factor, wherein said cell is ale to support any sub-genomic viral replication. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

5. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte

Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

6. 1). Nature of the invention, 2). Scope of claims, 3). State of art, 4). Level of skill in the art, 5). Unpredictability of the art, 6). Number of working examples, 7). Amount of guidance presented in the specification.

7. In the instant case, the nature of the invention is drawn to a cloned Huh-7 cell line and a method for making said cell line comprising transfection of Huh-7 cell line with a dominant negative disabling PKR mutation of Lysin at the amino acid residue 296 being replaced with Arg (PKR^{296}) and further with a HCV sub-genomic replicon, wherein said cell line is able to support the replication of sub-genomic HCV viral replicon and increase the viral replication. However, the scope of the claims read on a method for generating any cell line comprising any kind of dominant negative disabling mutation for any host cellular housekeeping genes and gene products that are used by the virus in replication cycle (See specification on lines 23-27), and any viral sub-genomic replicon, wherein said cell is able to increase any anti-viral response factor, wherein said cell is ale to support any sub-genomic viral replication.

8. The state of art teaches that there are many host genes involved in the host anti-viral response. PKR is only one kind of cellular factor among them, and not all host cellular factor with a dominant-negatively disabling mutation is able to successfully knockout in any cell line. , wherein said cell is able to increase any anti-viral response factor, wherein said cell is able to support any sub-genomic viral replication without influence the viability of a host cell, and also enhances the replication of a viral subgenomic replicon. For example, CCR5 is involved in HIV retroviral infection, a dominant negative mutation in CCR5 reduce the change or HIV viral replication, and it has nothing to do with HCV sub-genomic replicon's replication as evidenced by Glas et al. (Clinical Immunology 2003, vol. 108, pp. 46-50, see entire document). Sambhara et al. (Cellular Immunology 1998, Vol. 187, pp. 13-18) teach that a mice with a knock out of a cellular factor gene, i.e. perforin, which mediates the host T cell against virus infection, generate about 100-fold greater serum antibody response than wild-type mice. Furthermore, immune spleen cells from perforin know-out mice secret over 10-fold more INF-γ following in vitro re-stimulation than that of immune spleen cells from the normal control mice (See abstract).

9. Moreover, it is also unpredictable that every cell line is ale to be used for support the HCV sub-genomic replicon replication because the state of art teaches although the production of infectious virus from cells transfected with cDNA (RNA generated by an in vitro transcription of a cloned DNA copy of the viral genome) has been described for several plus-strand RNA virus, this approach turned out to be very difficult for HCV. Up to now the replication of a transfected HCV genome can only be succeed in tow human hepatoma cell line Huh-7 or hepG2. it suggests that the replication of HCV replicon may depend on distinct cellular factors (See Bartenschlager et al. J. Gene. Viro. 2000, Vol. 81, pp. 1631-1648, especially on page 1638, 1st column, lines 11-13 and page 1639, last paragraph on 2nd column).

10. The specification only hypothetically mentions a few genes that may be able to be mutated. But there is no any example or guidance showing how to make each of cell house keeping genes that involved in the viral replication to become dominant negatively disabling mutated, whether each of such gene mutation can be successfully transfected into any cell line, wherein said cell line is able to support any viral replicon replication. The only example that specification teaches is to make a substitutive mutation at the amino acid residue 196 from Lys to Arg in PKR gene, and than transfect said PKR mutant to Huh-7 cell to support enhancement of a HCV sub-genomic replicon replication in said cells.

11. Because the broad scope of the claims read on a method for generating any kind of cell with any host cellular gene proteins or other molecule gene dominant negative mutation, a person skill in the art require enormous top knowledge and technique at the PhD level to practice the full scope of the invention without certainty of success.

12. Given the above analysis of the factors which the courts have determined are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to have conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 101

13. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. The invention of claims 28-31 is directed to non-statutory subject matter. There is no recitation of isolation or synthesis in front of the claimed compound. Therefore, the claimed compound read on naturally occurring materials, which are considered to be non-statutory and non-patentable subject matter within the scope of 35 U.S.C. 101. See Official Gazett, 1077 O.G. April 21, 1987. It is recommended that the claim incorporate the claim language, " isolated" to overcome this rejection.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-4, and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Terenzi et al. (Nucleic Acids research 1999, Vol. 27, No. 22, pp. 4369-4375).

17. Terenzi et al. teach several cell lines transformed with dominant negative mutated PKR (PKR-/-), the transformed cell line is further transfected with a plasmid or pCMV-REP-Laz vector or other viral vector that contains Semliki Forest Virus replicon (See section of Materials and Methods and pages 4369-4370). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1-4, 10-11, 15-16, 20-21, 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terenzi et al. (Nucleic Acids research 1999, Vol. 27, No. 22, pp. 4369-4375) and Lohmann et al. (Science 1999, Vol. 285, pp. 110-113).

20. The claimed invention is drawn to a Huh-7 cell line comprising a dominant negative PKR mutation and sub-genomic HCV replicon and method of making said cell line in order to support the replication of sub-genomic HCV sub-genomic replicon.

21. Terenzi et al. teach several cell lines transformed with dominant negative mutated PKR (PKR-/-), the transformed cell line is further transfected with a plasmid or pCMV-REP-Laz vector or other viral vector that contains Semliki Forest Virus replicon (See section of Materials and Methods and pages 4369-4370). The disabling dominant negative mutation of the PKR is made by substitute the amino acid residue of lysine at position 269 to Arg. While Terenzi et al. do not teach to use said cell line to support the HCV replicon mutation, they conclude that the host cell enzymes that have evolved to control viral infections also limit the efficiency of gene expression systems. PKR-/- cells may prove useful for obtaining proteins from difficulty to express genes and may even increase production of protein therapeutic agents compared with culture available cell culture systems. Therefore, suppression of PKR is a promising approach for enhancing gene expression from viral- and non-viral-based vectors.

22. Lohmann et al. teach a HCV sub-genomic replication system that use Hu-7 cell for express the HCV gene products. However, the efficiency of protein expression by such HCV sub-genomic is rather limited (See entire document)

23. Therefore, in order to establish a efficient HCV sub-genomic replicon expression system, an ordinary skill in the art at the time of the invention was filled would have been motivated by the recited references and to combine the methods taught by Terenzi et al. and Lohmann et al. to established an enhanced HCV sub-genomic replicon expression system in Huh-7 cell by inactivating the gene of PKR and let the HCV sub-genomic replicon be able to express more efficiently cause by the PKR inactivation. As there are no unexpected results have been

provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BAOQUN LI, MD
PATENT EXAMINER

Bao Qun Li

1/05/2006

Baogun Li